

Attorney Docket No.: **DEX0531US.NP**
Inventors: **Wolfert et al.**
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REMARKS

Claims 1-4, 8-9, 12, 17, 19, 22, 25-27, 30, 35-36, 39, 42-45, 48, 51-52, 55, 59, 61, 64, 67-70, 73-74, 76, 78, 80-82 and 86-89 are pending in the instant application. Claims 1-4, 8, 9, 12, 17, 19, 22, 25-27, 30, 35, 36, 39, 42-45, 48, 51, 52, 55, 59, 61, 64, 67-70, 81 and 88 have been withdrawn from consideration by the Examiner. Claims 1-4, 8, 9, 12, 17, 19, 22, 25-27, 30, 35, 36, 39, 42-45, 48, 51, 52, 55, 59, 61, 64 and 67-70 have been canceled without prejudice by Applicants herein. Claims 73, 74, 76, 78, 80, 82, 86-87 and 89 have been rejected. Claim 73 and 86 have been amended. New claims 92-103 have been added. Support for these amendments is provided in the specification at, for example, page 20, line 28 through page 21, line 24, as well as in the original claims. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Finality of Restriction Requirement and Affirmation of Species Election

MPEP 808.01(a) states that an election of species should be made when a generic claim recites such a multiplicity of species that an unduly extensive and burdensome search is required. Applicants do not believe that directing the search to any

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substrate for Lp-PLA2 used in accordance with the claimed method or kit is either extensive or overly burdensome.

Accordingly, reconsideration of this species election requirement is respectfully requested.

However, in an earnest effort to be completely responsive, Applicants affirm election of the species 2-thio PAF, with traverse. Claims 73, 74, 76, 78, 80, 82, 86, 87 and 88 as well as new claims 92-103 read on this species. The Examiner has withdrawn claim 81 and 88 suggesting that these claims do not read on the elected species.

In accordance with MPEP § 809.01 and 37 C.F.R. § 1.146, it is respectfully pointed out that the claims should only be restricted to the species if no generic claim is held allowable.

Accordingly, upon allowance of the generic claims, it is respectfully requested that claims 81 and 88 be rejoined.

The Examiner has made final the Restriction Requirement mailed September 18, 2009 and withdrawn from consideration non-elected claims 1-4, 8, 9, 12, 17, 19, 22, 25-27, 30, 35, 36, 39, 42-45, 48, 51, 52, 55, 59, 61, 64, and 67-70. Thus, in light of the finality of this Restriction Requirement, Applicants have canceled without prejudice the non-elected claims. Applicants reserve the right to file a divisional application(s) to the

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canceled subject matter.

**II. Rejection of Claims 73, 74, 78, 80, 82, 86-87 and 89 under
35 U.S.C. 112, second paragraph**

Claims 73, 74, 78, 80, 82, 86-87 and 89 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner suggests that step (b) of claim 73 is vague and indefinite because it is confusing and unclear as to whether in step (b) the substrate is first converted to free thiol produced by the enzymatically active Lp-PLA2 before contacting the incubated mixture of step (a) or the incubated mixture of step (a) is contacted with the substrate in the presence of the enzymatically active Lp-PLA2.

Further with respect to step (b) of claim 73 and claim 86, the Examiner suggests that recitation "in the presence of enzymatically active Lp-PLA2" does not clearly indicate the relationship of the substrate to the presence of enzymatically active Lp-PLA2.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 73 to make clear the order of the steps of the claimed method. Further claim 73 has

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been amended to recite that the incubated sample is contacted with a substrate that is converted to an active thiol product by enzymatically active Lp-PLA2 when enzymatically active Lp-PLA2 is present in the sample. Claim 86 has been amended to recite a substrate that reacts with enzymatically active Lp-PLA2 to produce a detectable product.

Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of Claims 73, 74, 78, 80, 82, 86-87 and 89 under 35 U.S.C. 112, first paragraph - Written Description

Claims 73, 74, 78, 80, 82, 86-87 and 89 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner suggests that claims 73 and 86 recite "a compound which reduces active thiol(s)" while the specification only describes DTNB.

Applicants respectfully traverse this rejection.

MPEP 2163 states "The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, para. 1, for lack of adequate written description."

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MPEP 2163 further states "the examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96.

In the instant Office Action, at page 6, the Examiner has acknowledged that other thiol reducing agents are well-known. Accordingly, the evidence presented by the Examiner in the instant case is actually supportive that a person skilled in the art would recognize that the written description of the invention provides support for claims drawn to compounds [in addition to DTNP] which reduce active thiol(s) in the sample. As procedures and compounds for reducing active thiol(s) are well known to those skilled in the art, the absence of such specific details in the instant specification cannot be the basis for a lack of written description rejection. See MPEP 2163.

Withdrawal of this rejection is therefore respectfully requested.

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**IV. Rejection of Claims 73, 74, 78, 80, 82, 86, 87 and 89 under
35 U.S.C. 103(a)**

Claims 73, 74, 78, 80, 82 and 86 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui et al. (J. Lipid. Res. 1984) in view of Murata et al. (Chem. Phar. Biol. 1991). The Examiner suggests that since the thioester 2-thio-PAF is taught by Murata et al. to be useful as a substrate for PAF-AH, it would be obvious to one of ordinary skill in the art at the time the invention was made to consider using 2-thio-PAF of Murata et al. in the method of Farooqui et al. for spectrophotometric detection of PAF-AH in a sample.

Claims 86, 87 and 89 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui et al. in view of Murata et al. as described above and further in view of Maret et al. (U.S. Patent 5,478,741). Maret is cited for its teaching of putting assay components in a kit.

Applicants respectfully traverse this rejection.

At the outset, it is respectfully pointed out that claim 73 has been amended to recite a method for measuring enzymatically active Lipoprotein-associated Phospholipase A2 (Lp-PLA2) in a sample comprising the following steps in the order stated:

- (a) incubating the sample with a compound which reduces

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active thiol(s) in the sample for a time sufficient for said compound to reduce said active thiol(s);

(b) contacting the incubated sample with a substrate that is converted to an active thiol product by enzymatically active Lp-PLA2 when enzymatically active Lp-PLA2 is present in the sample; and

(c) measuring free thiol product indicative of enzymatically active Lp-PLA2 in the sample.

Accordingly, in the instant claimed invention, enzymatically active Lp-PLA2 is directly determined from the sample by measurement of free thiol product. Direct determination of enzymatically active LP-PLA2 in the sample in accordance with the instant claimed method and kit, without requirement of subtraction of values from a blank, is clearly supported by Example 2 of the instant specification.

In contrast, in the Farooqui method, free thiol product is not indicative of enzymatically active enzyme in the sample. Instead, the additional step of subtraction of a blank (background DTNB) is required. See specifically, page 1557, second column, 2nd sentence wherein Farooqui states "Nonenzymic background activity due to substrate migration is...subtracted from the observed reaction rate to yield the actual enzymatic

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activity."

Thus, the cited combinations of Farooqui et al. and Murata et al., and Farooqui et al., Murata et al. and Maret et al. do not arrive at the instant claimed invention and thus cannot render the instant claimed invention obvious.

Further, Applicants are submitting herewith a Supplemental Information Disclosure Statement inclusive of the package insert from the commercially available Cayman PAF Acetylhydrolase Assay Kit used today. Page 13 of the Cayman kit package insert, step 2 states: "Determine $\Delta A_{14}/\text{min.}$ for the no-enzyme controls (Blanks) and subtract this rate from that of the sample wells." This value is then used in step 3 to determine the PAF-AH activity. Thus, the same subtraction method described by Farooqui in 1984 is the method used today in the commercially available Cayman PAF Acetylhydrolase Assay Kit.

Thus, in no way are the instant claimed method and kit, which allow for calculating Lp-PLA2 activity directly from the absorbance detected in the sample alone, without a subtraction step, an obvious variation of the teachings of Farooqui et al. and Murata et al.

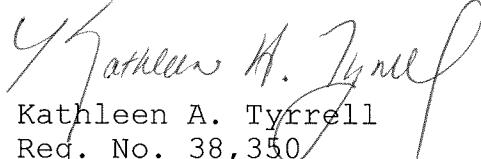
Withdrawal of this rejection under 35 U.S.C. 103(a) is respectfully requested.

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V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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